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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,633	11/13/2003	Pamela Pavco	MBHB02-325-A (400.047US)	6362

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,633	PAVCO ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-21-04; 11-08-04*. 8-11-05 & 7-18-05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claim 1 is objected to because of the following informalities: it recites the word "complementarity" which, based on grammatical English and claims 34 and 36, apparently should be "complementary". Appropriate correction is required.

Specification

2. The use of the trademark ANGIOZYME™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Information Disclosure Statement

3. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ...

must be submitted on a separate paper." Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

A copy of the Foreign Patent Document No. JP 08208687 (Hotoda et al.) was not provided, a copy of Application No. JP 08-208687, was provided, however this document does not include Hotoda et al. as the inventor, and the subject matter of the provided reference is not related to the instant invention.

Additionally, the International Search Reports included in the IDS were reviewed, however, the documents listed in the International Search Reports are not considered publications complying with 37 CFR 1.98. Therefore, the references cited in the Search Reports have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609 subsection III. C(1).

Priority

4. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/138,674, 09/870,161, 09/708,690, 09/371,772, 08/584,040, and 60/005,974, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the cited references do not provide support for siRNA, or dsRNA targeting VEGFR-2. Therefore, the priority date granted to Applicants is that of provisional application 60/334,461, the provisional application provides adequate support for the instantly claimed invention.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

7. Claims 1-17 are drawn to short interfering RNA molecules (siRNA) that comprises a first nucleotide sequence complementary to RNA sequence encoding vascular endothelial growth factor 2 or a portion thereof, wherein by RNA interference, wherein said first nucleotide sequence comprise from about 19 nucleotides to about 23

nucleotides. Claims 2-17 limit claim 1 by reciting physical characteristics of the siRNA such as number of nucleotides, presence of overhanging nucleotides and modifications to the siRNA such as phosphorothioates and terminal cap structures. Since the claims are not limited to any particular nucleotide sequence encoding VEGFR2, and the use of the phrase "or a portion thereof," gives claim 1 a broad scope that encompasses siRNA that target VEGFR2 from any species as well as any isoform or variant of VEGFR2 from any species.

8. The specification mentions siRNA targeting VEGFR2 briefly on pages 34-36. However, the specific embodiments of the invention described in the examples, and the detailed description of the invention is specifically directed to ribozymes targeting VEGFR1 or VEGFR2. The specification as filed does not describe any single siRNA targeting specifically VEGFR2. Moreover, there is no disclosure found in the specification or known in the art that relates the structure of an siRNA directed to VEGFR2 that function to down regulate in all species, or down-regulating isoforms or variants of VEGFR2 genes from all species.

9. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

10. MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

11. The skilled artisan cannot envision the detailed structure of the encompassed siRNAs directed to any VEGFR2, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

12. The species of VEGFR2 ribozymes specifically disclosed are not representative of the genus of VEGFR2 siRNA because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavco et al. (WO 97/15662), Robinson et al. (WO 95/04142), Jellinek et al. (1994), Rockwell et al. (WO 95/21868), and Yu et al. (1998), in view of Hammond et al. (Nature Genetics 2001, Vol. 2:110-119), Elbashir et al. (Genes and Development, 2001 Vol. 15:188-200), and Parrish et al. (Molecular Cell, 2000 Vol. 8:1077-1087).

16. Pavco et al., describes methods and reagents for treating diseases or conditions related to levels of vascular endothelial growth factor receptor.

Robinson et al. describes the use of certain compositions comprising antisense oligonucleotides targeted against VEGF RNA to inhibit VEGF expression, and a pharmaceutically acceptable carrier (e.g. DOTAP, see page 21).

Jellinek et al. (1994) describe the use of specific VEGF-specific high-affinity RNA aptamers to inhibit the binding of VEGF to its receptors.

Rockwell et al. describe the use of certain anti-VEGF receptor monoclonal antibodies to neutralize the effect of VEGF on endothelial cells.

Yu et al. describe the nucleic acid sequence of vascular endothelial growth factor receptor 2 (KDR) from humans.

Neither Pavco et al., Robinson et al., Jellinek et al., Rockwell et al., or Yu et al. teach an interfering RNA molecule that down regulates expression of a VEGFR 2 gene by RNA interference.

Hammond et al. teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense. On page 110, first column, Hammond teaches that antisense methods are straightforward but suffer from "questionable specificity and incomplete efficacy". RNA interference on the other hand, "has been shown in diverse organisms to inhibit gene expression in a sequence-specific manner" (same page and column) and requires only a few molecules of dsRNA per cell to silence expression. Hammond also teaches that the RNA interference phenomenon in animals was

discovered by researchers who were using antisense techniques and found that the use of double stranded instead of single-stranded RNAs reduced gene expression tenfold more efficiently (see paragraph bridging pages 110-111). Hammond et al. do not teach use of siRNAs.

Elbashir et al. teach that RNA interference is mediated efficiently by synthetic RNAs that are 21-22 nucleotides in length and name these short duplexes "short interfering RNAs" (siRNAs). Elbashir et al. also teach that 21-23 nucleotide RNAs are implicated as the guide RNAs for target recognition in RNA interference.

Parrish et al. teach that some common nucleotide modifications, including phosphorothioate, sugar modifications (e.g. 2'-fluorouracil, and 2'-deoxycytidine, see page 1081, 2nd col.) and terminal cap structures are well tolerated in interfering RNAs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a short interfering RNA (siRNA) molecule that down regulates expression of VEGFR-2 gene by RNA interference using the sequence taught by Yu et al. One of ordinary skill in the art would have been motivated to make this modification because Pavco et al., Robinson et al., Jellineck et al., and Rockwell et al. describes the use of various inhibitors to reduce the expression of VEGF receptor expression or its ligand VEGF for the purpose of treating conditions associated with the expression of these genes, while Hammond et al. provide the motivation to use RNA interference for purposes of specificity and inhibition efficiency. Additionally, Elbashir et al. provide a motivation to make a short teaching that a siRNA is an efficient mediator of RNA interfering RNA interference.

One of ordinary skill in the art would have had a reasonable expectation of success in making a siRNA to down-regulate expression of a VEGFR-2 mRNA by siRNA because Hammond et al. teach that RNA interference is a method to regulate gene expression and Elbashir teach that short duplex RNAs mediate RNA interference. One of ordinary skill in the art would have been motivated and expected success in modifying the siRNA since Parrish et al. taught nucleotide modifications are well-tolerated in interfering RNA molecules.

Thus, the invention of claims 1-17 would have been obvious, as a whole at the time of invention.

Conclusion

17. No claimed allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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